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Cuff pressure pain detection is associated with both sex and physical activity level in non-athletic healthy subjects

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ABSTRACT

Purpose

The aim of this study was to evaluate pressure pain sensitivity on leg and arm in 98 healthy persons (50 women) using cuff algometry. Furthermore associations with sex and physical activity level were investigated.

Method

Normal physical activity level was defined as Godin Leisure-Time Exercise Questionnaire (GLTEQ) score ≤45 and high activity level as GLTEQ >45. A pneumatic double-chamber cuff was placed around the arm or leg where a single chamber was inflated. Cuff inflation rate (1 kPa/s) was constant and the pain intensity was registered continuously on a 10-cm electronic Visual Analogue Scale (VAS). The pain detection threshold (PDT) was defined as when the pressure was perceived as painful and pain tolerance (PTT) was when the subject terminated the cuff inflation. For PTT the corresponding VAS score was recorded (VAS-PTT). The protocol was repeated with two chambers inflated.

Result

Only *single cuff* results are given. For women compared to men, the PDT was lower when assessed in the arm ($P=0.002$), PTTs were lower in the arm and leg ($P<0.001$), and the VAS-PTT was higher in the arm and leg ($P<0.033$). Highly active participants compared with less active had higher PDT ($P=0.027$) in the leg. Women showed facilitated spatial summation ($P<0.014$) in the arm and leg and a steeper VAS slope (i.e. the slope of the VAS-pressure curve between PDT and PPT) in the arm and leg ($P<0.003$).

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Conclusion

This study indicates that reduced pressure pain sensitivity is associated both with male sex and physical activity level.

Keywords: Experimental pain, Pain assessment, Cuff pressure sensitivity, Physical activity, Sex, Gender

ABBREVIATIONS

BMI	Body mass index
BP	Blood pressure
GLTEQ	Godin Leisure-Time Exercise Questionnaire
HAM	Highly active men
HAW	Highly active women
NAM	Normally active men
NAW	Normally active women
PDT	Pain detection threshold
PPT	Pressure pain threshold
PTT	Pain tolerance threshold
SEM	Standard error of the mean
SR	Spatial summation ratio
SS	Spatial summation
VAS	Visual analogue scale
VAS-PTT	VAS score at pain tolerance threshold

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INTRODUCTION

Sensitivity to experimental pressure pain is strongly associated with sex and to some extent physical activity, likewise age seems to play a significant role (1). Physical activity influences the pain perception (2, 3) although the duration and intensity of physical exercise needed to modulate pain sensitivity is not known in detail (4). Reduced pain sensitivity and decreased pain reports have been found during and after different types of experimental exercises (4, 5). Exercise-induced hypoalgesia is most pronounced at a strenuous level (6) and may depend on the degree of individual pain sensitivity (7). The underlying mechanisms of how strenuous physical activity modulates pain perception are not fully understood. Recent data supports peripheral localized effects of physical exercise on pain modulation, showing changes in the equilibrium between intramuscular algesic and analgesic substances after a longer period of physical exercise (8). Other explanations include descending control mechanisms via the endogenous opioid system or stimulation of baroreceptors by increases in blood pressure (9) resulting in more widespread sensitivity changes. Moderate physical activity is also known to increase the conditioned pain modulation demonstrated as a larger increase in pain thresholds in response to a conditioning pain stimulus (10). Tesarz et al. showed in a study of endurance athletes compared to normally active controls that athletes were significantly less sensitive to mechanical pain but that the conditional pain modulation was less activated, suggesting that this system may be less responsive (11). Athletes seem to develop long-term effects in pain processing mainly with respect to increased tolerance to mechanical stimuli, whereas pain thresholds show inconsistent changes (2). Increased ischemic pain tolerance but unchanged pressure pain thresholds (PPT) after aerobic exercise during six weeks have been reported (3). In a study by Goodin et al. the level of pain catastrophizing turned out to be an important mediator for reduced evoked pain reactions in individuals who performed a greater amount of

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strenuous physical activity per week (12). Thus, based on the literature the level of physical exercise seems to be associated with different mechanisms relevant for the pain sensitivity. Generally women demonstrate increased sensitivity to most pain stimulation modalities (i.e. thermal and pressure) compared to men (13-15). However regarding perceived pain intensity and unpleasantness there is no clear association with sex (13). Women have decreased pressure pain thresholds as well as thermal pain tolerance compared with men (13, 16, 17). Hormonal influence may affect the pain sensitivity and a recent study using functional magnetic resonance imaging showed that pain-related neural processing varies across the menstrual cycle (18). However, the role of circulating sex hormones in modulation of pain perception is still unclear (18, 19). Psychosocial factors such as differences in coping strategies and sociocultural beliefs about femininity and masculinity may play a role in sex differences in pain sensitivity (20, 21)

For some pain modalities there are regional body differences in pain sensitivity demonstrated for both single-point and cuff pressure (1, 22) and thermal thresholds (15). The specific mechanism behind regional differences in sensitivity is unknown although the degree of overlapping receptive fields may play a role (1). Computerized cuff pressure algometry (CPA) mainly asses the pain sensitivity of deep somatic tissue, is reliable and less biased by inter and intra-examiner variability than conventional algometry technique (23-25).

Based on our previous study on tonic pain we hypothesized that being a woman or having a low level of physical activity were associated with increased pain sensitivity to pressure. The aim was to investigate if even moderate differences in physical activity were associated with differences in acute cuff pressure pain sensitivity. A secondary aim was to look for regional differences (i.e. arm vs. leg).

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MATERIAL AND METHODS

Subjects

This article is the second report from a sample of healthy people previously investigated regarding tonic cuff pressure sensitivity, anthropometric data are presented in Table 1 (22). The subjects were recruited through advertisement in the local newspaper. Both normally trained and well sports trained subjects were recruited. Their inclusion criteria were age between 20 and 65 years, and pain-free. A brief medical history was taken that included any current or previous presence of musculoskeletal pain or discomfort. Power analysis for this study suggested a sample size of 50 individuals in each group when looking for gender differences (assuming a difference of 10 kPa between means). We hypothesized a similar sample size would be sufficient for detecting differences related to physical activity level (Power 0.8 and two-tailed significance level $P<0.05$). The study was conducted in accordance with the Declaration of Helsinki. The study was granted ethical clearance by the Linköping University Ethics Committee (2011/102-31), and all participants gave informed written consent. The subjects of received 400 SEK as compensation for their participation in the study.

Experimental protocol

The dominant “writing hand” side was chosen for all assessments in line with previous studies (22, 26). All assessments were made in one session. Blood pressure in the right arm, weight and height were recorded. Cuff algometry with first single and then double-chamber cuffs were completed on the arm and then on the leg. All assessments were repeated twice at each site, and the mean was calculated for further analysis. A short (<5 min) break was allowed when switching the cuff from arm to leg.

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Physical activity level

Godin Leisure-Time Exercise Questionnaire (GLTEQ) was used to estimate the physical activity level. It contains four questions where the person states how many times weekly he/she is doing “strenuous”, “moderate” and “mild” exercise, respectively. The different intensities are described with examples in the questionnaire. A total leisure activity score is calculated by multiplying the number of times per week with 9 for strenuous, 5 for moderate and 3 for mild exercise. A high score indicates higher intensity and higher frequency of weekly leisure-time activities (27, 28). Normal physical activity level was defined as GLTEQ scores less than or equal to the median of GLTEQ scores for all subjects (i.e. 45). Consequently, subjects with GLTEQ scores higher than the median GLTEQ score were categorized as the high activity group.

Cuff algometry

The experimental setup consisted of a double chamber 13-cm wide tourniquet cuff (a silicone high-pressure cuff, separated lengthwise into two equal-size chambers; VBM Medizintechnik GmbH, Sulz, Germany), a computer-controlled air compressor, and an electronic visual analogue scale (NociTech and Aalborg University, Denmark). The compression rate of the compressor was 1 kPa/s and controlled by the computer. The cuff was connected to the compressor and wrapped around the mid-portion of the triceps surae muscles of the leg or around the heads of biceps and triceps muscles of the arm. The maximum pressure limit used was 100 kPa (760 mmHg). The stimulation could be aborted at any time by the subject using a push button or by the experimenter via the computer or the pressure release button.
The pain intensity was simultaneously recorded using the 10-cm electronic VAS and sampled at 10 Hz. The subject adjusted the VAS score via a variable lever and the magnitude was displayed on a red light bar fully visible to the subject. Zero and 10 cm extremes on the VAS

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were defined as "no pain" and as "worst possible pain", respectively. Pain detection threshold (PDT; kPa), pain tolerance threshold (PTT; kPa), and pain tolerance pain intensity (VAS-PTT; cm) were extracted. PDT was defined as the pressure equivalent to the moment of transition from strong to painful pressure (i.e. VAS > 0.1 cm for the first time). PTT was defined as the pressure level where the subject felt a pain sensation strong enough to feel like interrupting or stopping the session, at which point subject did so by pressing the stop button (29). VAS-PTT was defined as the pain intensity (VAS) corresponding to PTT. Moreover, the slope of the VAS-pressure curve between PDT and PTT pressures was calculated based on raw data. A steep slope was considered a sign of high pain sensitivity (i.e. PTT is reached faster relatively to PDT).

The degree of spatial summation was investigated calculating a summation ratio (SR) for PDT and PTT (the pressure measured with single cuff inflation was divided by the corresponding values using double cuff inflation). Thus, a higher SR indicated more spatial summation of pain.

Statistics

Statistical analyses were made using IBM SPSS (version 21.0; IBM Corporation, New York, USA) and $P \leq 0.05$ was used as level of significance. Data in text and tables are presented as mean ± standard deviation together with 95% confidence interval (95%CI) for the mean. We used non parametric tests since the requirements for a two-way ANOVA of the cuff algometry data were not fulfilled. Hence, Mann Whitney U test was used to compare groups with respect to sex and activity level respectively. The Kruskal-Wallis test was used for comparisons between four groups (sex and activity level combined); if significant posthoc pairwise comparisons were made. Wilcoxon Signed Rank test was used when comparing arm and leg.

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RESULTS

Overview of experimental findings during pain stimulation is presented in figure 1.

(Space for Fig. 1) Note; please observe that the additional legend A, B and C with text should be placed BELOW the actual figure. This works if the figure is pasted between the upper and lower legends.

Pain detection thresholds

PDT to single cuff stimulation in the arm showed a significant sex difference; PDT for double cuff stimulation of the arm nearly reached significance (p=0.052) (**Table 2**). PDT for single cuff of the leg showed a significant difference with respect to activity level i.e. higher PDT of the leg in the highly active group.

Pain tolerance thresholds

Significant sex differences in PTT of the arm and leg both for single and double cuff were found and with lower PTT in women (**Table 3**). No significant group differences existed with respect to activity level (**Table 3**). Hence, the statistical comparisons between the four groups (i.e. HAM, NAM, HAW and NAW) mainly reflected the sex difference; the two groups of men had highest PTTs, HAW was generally intermediate PTTs while NAW had the lowest PTTs.

In the arm 65-69 percent of the subjects reached the maximum pressure limit 100kPa and in the leg 29-54 percent. The lower fraction reported was during double cuff stimulation, both in the arm and the leg.

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VAS scores at pain tolerance thresholds

Significant sex differences were found for VAS-PTT with higher VAS scores for women at PTT for single cuff both in the arm and in the leg and for double cuff in the arm (**Table 3**). The VAS-PPT variables did not differ significantly with respect to activity level. The statistical comparisons between the four groups mainly reflected the sex difference; the two groups of men had lowest VAS-PTTs, HAW had intermediate VAS-PTTs and NAW had the highest VAS-PTTs (**Table 3**).

Spatial summation ratio

Significant sex differences were found for SR both in the arm and in the leg; women having higher ratios (more spatial summation) than men at PTT (**Table 3**). No significant differences in SR with respect to activity level were found (**Table 3**)

Slope

The VAS slopes were significantly steeper for women than men both in the arm and leg with single and double cuff (**Table 4**). No effect of activity level was seen.

Comparisons between arm and leg

PDT for double cuff was lower in the leg than in the arm ($P<0.001$), the same was true for both PTTs with single cuff ($P<0.001$) and double cuff ($P<0.001$). SR of PDT and PTT were significantly higher in the leg than in the arm (both $P<0.001$). VAS-PTTs for single and double cuff were higher in the leg than in the arm (both $P<0.001$). VAS slopes both for single ($P<0.001$) and double cuff ($P<0.001$) were steeper in the leg than in the arm.

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DISCUSSION

Being a woman was associated with increased pain sensitivity and facilitated spatial summation in the arm and leg. Higher physical activity level was associated with increased PDT (hypoalgesia) in the leg for both women and men.

Decreased leg pain sensitivity associated with physical fitness

Previous findings suggest an association between *strenuous exercise* and increased tolerance to pain (5, 6). Increased cuff PDTs in the leg for highly active subjects is consistent with increased pressure pain thresholds (PPT) on leg muscles presented in a previous study on this group of healthy subjects (22). PDTs as defined with cuff algometry can be regarded as a psychophysical equivalent to pressure pain thresholds (PPT) assessed with handheld algometry although the distribution of stress-/strain in the tissue is deeper and the tissue volume stimulated larger with cuff algometry (30). One reason why physical fitness in this group of people is associated with pain detection in the leg could be related to the assumption that most every-day training at a non-athletic level involves proportionally more musculature in the legs than in the arms (e.g. walking and jogging). In contrast to the present findings Tesarz et al. suggested that exercise at an athletic level mainly affects pain tolerance, since athletes are forced to develop efficient pain-coping skills because of their systematic exposure to periods of intense pain (2). For subjects exceeding 100 kPa in pain tolerance we used a conservative estimate of PTT, this limited the variation of data and reduced the possibility to detect differences in the higher span of pain tolerance thresholds. The choice of cut-off level for normal or high physical activity can also play a role in this respect, in this case the median and mean values for GLTEC were close (i.e. 45.5 and 47.8 respectively). Another reason for the lack of significant effect of physical fitness on PTT could be related to insufficient power (i.e., the actual mean difference turned out to be 5 kPa instead of the calculated 10 kPa).

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Furthermore only a questionnaire may not reflect the actual level of regular physical activity or fitness, adding oxygen uptake methodology or accelerometer recordings could improve this aspect. Non-strenuous exercise may activate different mechanisms involved in acute pain modulation than exercise at athletic and strenuous levels, since the effect observed in this study is regional it speaks in favour of mechanisms related to peripheral tissue and nociception.

Pressure pain sensitivity increased in women

An important factor affecting pain sensitivity is sex (14, 31) and since we did not have strenuous exercise as an independent factor in this study, the effects of sex may have overridden any effects of physical fitness (i.e., either to low intensity or short duration) which strengthens the already strong association between sex and pain sensitivity. The finding of generalized increased spatial summation in women compared to men is unexpected although facilitated temporal summation has been indicated for women with cuff-algometry (1). Spatial summation of heat pain has been investigated by Lautenbacher et al. but no effect of sex could be established (32). The present findings are worth taking into account when designing studies and analysing data. The finding that even the VAS-PTT is higher for women is logical and goes hand in hand with decreased tolerance. A steeper VAS-pressure slope is interpreted as a further sign of increased dynamic sensitivity seen in both arm and leg.

Increased cuff pain sensitivity in leg compared with arm

This finding has been corroborated in earlier studies where cuff measurements have been performed both in the arm and in the leg, in this study all five experimental measures pointed in the same direction (i.e., detection, tolerance, VAS-PTT, spatial summation and slope) (1, 22, 26). Furthermore higher thermal sensitivity in the leg has earlier been shown for women

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(15). In contrast, the relationship between sensitivity in the arm and in the leg is inverse when using manual pressure algometry (1). Hitherto, no special care or attention has been directed to the fact that different ways of assessing influence the outcome - especially when designing studies investigating differences in central pain modulation. The physiological mechanism behind this phenomenon is not known, but one can speculate that the excitation of more nociceptors (in the leg), regional differences in overlapping receptive fields (1), or even phylogenetic explanations are possible.

Conclusion

This study indicates that being a woman is associated with increased pain sensitivity and facilitated spatial summation in the arm and leg. Higher physical activity level is associated with hypoalgesia in the leg for both women and men.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: DL, TGN, LAN, BG and AS. Data collection: DL, AS and EBL. Analyzed the data: DL, AS, BB, BG and EBL. Wrote the first version of the paper: DL, BB and BG. Revised different versions of the manuscript including the final version: all authors.

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Figure 1: Overview of differences in pain thresholds and related measures. A) differences related to increased physical activity level (men and women), B) differences related to sex (women as compared with men), and C) differences related to anatomical region (leg as compared with arm for both men and women). Pain detection thresholds (PDT), Pain tolerance thresholds (PTT), VAS score at pain tolerance threshold (VAS-PTT), Spatial summation (SS), Slope of the VAS-pressure curve (Slope). Filled arrow indicates significant difference, unfilled arrow indicates no significant change

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A	B	C
High vs low activity	Women vs men	Leg vs arm

Tables

Table 1: Summary of earlier published age, anthropometric data, blood pressures and activity level (mean values ± 1SD and 95%CI for the mean) presented in four groups; women, men, normally active and highly active.

Groups Variables	Women (n=50) Mean ± 1SD (95%CI)	Men (n=48) Mean ± 1SD (95%CI)	NORMALLY ACTIVE (n=49) Mean ± 1SD (95%CI)	HIGHLY ACTIVE (n=49) Mean ± 1SD (95%CI)
Age	35.2±10.6 (32.2-38.2	33.6±11.1 (30.3-36.8)	35.8±12.1 (32.4-39.3)	32.9±9.3 (30.2-35.6)
Height (cm)	168±7 (166-170)	182±6 (180-183	176±9 (174-179)	173±9 (170-176)
Weight (kg)	65.0±8.3 (62.6-67.5)	81.4±8.8 (78.8-83.9)	76.3±10.7 (73.2-79.4)	70.2±12.2 (66.6-73.8)
BMI (kg/m^2)	23.1±2.7 (22.3-23.9)	24.7±2.3 (24.0-25.3)	24.5±2.5 (23.8-25.3	23.2±2.6 (22.5-24.0)
Systolic BP (mm Hg)	124±24 (118-131	134±12 (130-138)	128±10 (125-131)	131±26 (123-138)
Diastolic BP (mm Hg)	77±10 (74-80)	78±6 (76-80)	77±6 (75-78)	79±10 (76-81)
GLTEQ	48.7±23.7 (42.0-55.5)	46.9±28.8 (38.5-55.2)	27.4±10.9 (24.3-30.6)	68.2±20.5 (62.3-74.1)
GLTEQ4	1.5±0.6 (1.3-1.7)	1.3±0.8 (1.0-1.5	1.2±0.7 (0.95-1.3)	1.6±0.6 (1.4-1.8)

Body Mass Index (BMI); Blood pressure (BP); Godin Leisure-Time Exercise Questionnaire (GLTEQ); Exercise times/week (GLTEQ4).

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Table 2: PDT including spatial summation ratios; mean values ± 1 SD and 95% CI for the mean of the arm and the leg in highly active men (HAM), normally-active men (NAM), highly active women (HAW), and normally active women (NAW). The statistical analyses to the right were done with respect to sex, activity level and the four groups (including posthoc tests if appropriate), respectively.

Variables	HAM (n=22) Mean ± 1SD (95%CI)	NAM (n=26) Mean ± 1SD (95%CI)	HAW (n=27) Mean ± 1SD (95%CI)	NAW (n=23) Mean ± 1SD (95%CI)	Statistics Sex p-value	Statistics Activity level p-value	Statistics Four groups p-value	Post-hoc
Arm								
PDTsingle (kPa)	30.5±17.4 (22.8-38.2	28.4±12.9 (23.2-33.6)	21.2±12.5 (16.2-26.3	19.6±13.6 (13.7-25.5)	0.002*	0.732	0.020*	NAW NE NAM & HAM
PDTdouble (kPa)	34.5±20.6 (25.1-43.9)	30.5±18.0 (23.3-37.8)	29.9±20.4 (21.8-37.9)	20.4±13.3 (14.6-26.1)	0.052	0.165	0.076	
Spatial summation-ratio	0.95±0.35 (0.79-1.11)	1.11±0.61 (0.87-1.36)	0.82±0.31 (0.69-0.94)	1.26±1.6 (0.59-1.94)	0.475	0.126	0.340	
Leg								
PDTsingle (kPa)	34.1±21.0 (24.8-43.4)	19.7±11.1 (15.2-24.2)	24.9±17.4 (18.0-31.8)	19.2±12.3 (13.9-24.5)	0.261	0.027*	0.052	
PDTdouble (kPa)	24.1±15.7 (17.2-31.1)	16.8±10.4 (12.6-21.0)	20.6±14.9 (14.7-26.5)	16.3±11.2 (11.4-21.1)	0.392	0.066	0.210	
Spatial summation-ratio	1.51±0.70 (1.21-1.82)	1.29±0.64 (1.03-1.54)	1.26±0.48 (1.07-1.45)	1.14±0.46 (0.94-1.34)	0.382	0.192	0.314	

Pain detection threshold (PDT); * denotes significance; NE denotes non equal.

Table 3: PTT (kPa) and VAS-PTT (cm VAS at PTT) including spatial summation ratios; mean values (±SD) and 95%CI for the mean of the arm and the leg in the four groups; highly active men (HAM), normally-active men (NAM), highly active women (HAW) and normally active women (NAW). The statistical analyses to the right were done with respect to sex, activity level and the four groups (including posthoc tests if appropriate), respectively.

Variables	HAM (n=22) Mean ± 1SD (95%CI)	NAM (n=26) Mean ± 1SD (95%CI)	HAW (n=27) Mean ± 1SD (95%CI)	NAW (n=23) Mean ± 1SD (95%CI)	Statistics Sex p-value	Statistics Activity level p-value	Statistics Four groups p-value	Post-hoc
Arm								
PTTsingle (kPa)	94.9±14.2 (88.7-101.2)	98.8±5.4 (96.6-101.0)	90.2±15.7 (84.0-96.4)	80.0±22.9 (70.1-89.9	<0.001*	0.804	0.001*	NAW NE NAM & HAM; HAW NE NAM
PTTdouble (kPa)	92.2±1.4 (84.0-100.4)	96.3±10.9 (91.9-100.7)	84.3±23.6 (74.9-93.6)	75.2±27.0 (63.5-86.8)	0.002*	0.844	0.006	NAW NE NAM & HAM; HAW NE NAM
VAS-PTTsingle (cm)	4.6±3.2 (3.2-6.0)	5.9±2.7 (4.8-7.0)	7.0±2.9 (5.9-8.2)	7.4±2.5 (6.4-8.6)	0.001*	0.321	0.006*	HAM NE HAW & NAW; NAM NE NAW
VAS-PTTdouble (cm)	5.1±3.1 (3.7-6.5)	6.2±2.6 (5.1-7.2)	7.3±2.8 (6.3-8.5)	8.1±2.1 (7.2-9.0)	0.001*	0.322	0.007*	HAM NE HAW & NAW; NAM NE NAW
Spatial summation-ratio	1.07±0.21 (0.97-1.16)	1.04±0.11 (0.99-1.08)	1.22±0.83 (0.88-1.54)	1.11±0.16 (1.04-1.18)	0.014*	0.628	0.058	
Leg								
PTTsingle (kPa)	90.5±18.0 (82.5-98.5)	90.0±19.3 (82.2-97.8)	83.1±22.5 (74.2-92.0)	73.5±22.9 (63.6-83.4)	0.001*	0.327	0.002*	NAW NE HAW, NAM & HAM
PTTdouble (kPa)	81.1±23.8 (70.5-91.6)	81.2±24.9 (71.2-91.3	67.6±28.9 (56.2-79.0)	52.6±21.9 (43.1-62.0)	<0.001*	0.215	0.001*	NAW NE NAM & HAM
VAS-PTTsingle (cm)	5.7±3.6 (4.1-7.3)	7.2±2.5 (6.3-8.3	7.6±2.8 (6.5-8.7)	8.4±2.1 (7.5-9.3)	0.033*	0.095	0.046*	HAM NE NAW
VAS-PTTdouble (cm)	7.5±2.5(6.4-8.7)	8.8±1.6 (8.2-9.5)	8.3±2.3 (7.4-9.3)	8.4±2.2 (7.5-9.4	0.983	0.145	0.482	
Spatial summation-ratio	1.12±0.30 (0.98-1.25)	1.16±0.24 (1.07-1.26)	1.68±1.70 (1.01-2.26)	1.49±0.44 (1.30-1.68)	<0.001*	0.364	<0.001*	HAM NE HAW & NAW; NAM NE HAW & NAW

Pain tolerance threshold (PTT); VAS score at pain threshold tolerance (VAS-PPT); * denotes significance; NE denotes non equal.

Table 4: The VAS –pressure slope from the start (PDT) to the end of inflation (PTT); mean values (±1SD) and 95%CI for the mean of the arm and the leg in the four groups; highly active men (HAM), normally-active men (NAM), highly active women (HAW) and normally active women (NAW). The statistical analyses to the right were done with respect to sex, activity level and the four groups (including posthoc tests if appropriate), respectively.

Variables	**HAM (n=22)**	**NAM (n=26)**	**HAW (n=27)**	**NAW (n=23)**	**Statistics**	**Statistics**	**Statistics**	
	Mean ± 1SD (95%CI)	**Mean ± 1SD (95%CI)**	**Mean ± 1SD (95%CI)**	**Mean ± 1SD (95%CI)**	**Sex p-value**	**Activity level p-value**	**Four groups p-value**	**Post-hoc**
Arm								
Slope single ($cm{*}s^{-1}$)	3.6±3.1 (2.2-4.9)	3.9±2.1 (3.0-4.7)	5.8±3.4 (4.4-7.1)	7.0±4.1 (5.3-8.8)	<0.001*	0.408	0.002*	HAM NE HAW & NAW; NAM NE HAW & NAW
Slope double ($cm{*}s^{-1}$)	4.3±4.0 (2.5-6.0)	4.4±2.6 (3.4-5.5)	6.4±4.0 (4.8-8.0)	8.4±5.3 (6.1-10.7)	<0.001*	0.282	0.001*	HAM NE HAW & NAW; NAM NE NAW
Leg								
Slope single ($cm{*}s^{-1}$)	4.7±4.2 (2.9-6.6)	5.8±3.3 (4.4-7.1)	7.2±4.3 (5.5-8.9)	8.6±4.7 (6.6-10.6	0.003*	0.183	0.009*	HAM NE HAW & NAW; NAM NE NAW
Slope double ($cm{*}s^{-1}$)	7.8±6.1 (5.1-10.5)	8.8±4.7 (6.9-10.6)	10.7±6.0 (8.3-13.1)	11.9±6.5 (9.1-14.8)	0.005*	0.441	0.030*	HAM NE HAW & NAW; NAM NE NAW

1 min=60kPa;* denotes significance; NE denotes non equal.

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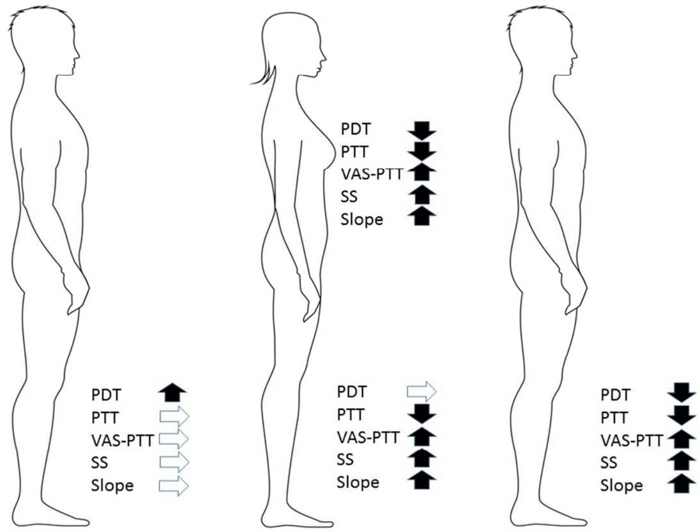

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